Science
AAAS

Globalization, Land Use, and the Invasion of West Nile Virus

A. Marm Kilpatrick

Science **334**, 323 (2011);
DOI: 10.1126/science.1201010

Globalization, Land Use, and the Invasion of West Nile Virus

A. Marm Kilpatrick

Many invasive species that have been spread through the globalization of trade and travel are pathogens. A paradigmatic case is the introduction of West Nile virus (WNV) into North America in 1999. A decade of research on the ecology and evolution of WNV includes three findings that provide insight into the outcome of future pathogen introductions. First, WNV transmission in North America is highest in urbanized and agricultural habitats, in part because the hosts and vectors of WNV are abundant in human-modified areas. Second, after its introduction, the virus quickly adapted to infect local mosquito vectors more efficiently than the originally introduced strain. Third, highly focused feeding patterns of the mosquito vectors of WNV result in unexpected host species being important for transmission. This research provides a framework for predicting and preventing the emergence of foreign vector-borne pathogens.

The growth of human populations and the development of rapid transportation systems have made the world's biota more connected than at any time in Earth's history. The result has been a breakdown in biogeographic barriers and the introduction of species into novel habitats. Globally, introduced invasive species are estimated to cause >$120 billion in damage annually (*1*) and include several pathogens that have direct impacts on the health of humans, livestock, and wildlife. Pathogens spread by trade and travel in the past 500 years include those causing the human diseases malaria, dengue, and HIV/AIDS; wildlife and livestock pathogens, such as anthrax, rinderpest, rabies, and avian malaria; and numerous diseases of crops and wild plants, including chestnut blight, potato blight, and sudden oak death (*2*, *3*). Introductions have continued with invasions by novel strains of influenza, severe acute respiratory syndrome, and West Nile virus (WNV), among many others. The factors that determine the outcome and impact of invasions are frequently complex and poorly understood (*4*, *5*); however, extensive research on WNV over the past decade has enabled a detailed exploration of its invasion, including pathways of introduction, interactions with the biotic and abiotic environment in the new region (Fig. 1), and impacts on ecosystem health.

WNV is a single-stranded RNA virus in the family Flaviviridae that includes several important humans pathogens: dengue, Japanese encephalitis, and yellow fever viruses (*6*). WNV was first isolated in 1937 from a febrile patient in Uganda, and subsequent studies showed that WNV transmission was endemic and widespread across tropical parts of Africa, southern Asia, and northern Australia, and episodic in more temperate parts of Europe (*7*). As with other vector-borne diseases, the warmer temperatures in the tropics facilitate longer transmission seasons and sometimes increased transmission intensity through faster mosquito and virus development and increased biting rates. In some populations in Africa, >80% of people over 15 years old have antibodies to WNV (*8*); however, WNV was previously considered nearly asymptomatic and in the 1950s was even tried as an anticancer therapy (*9*).

In 1999, WNV was introduced into North America, where it spread rapidly with major economic and public health consequences (*7*). The virus reached the west coast in only 4 years (Fig. 2), with regional epidemics in 2002 and 2003 and more localized epidemics occurring in other years. Between 1999 and 2010, ~1.8 million people were infected, with ~360,000 illnesses, 12,852 reported cases of encephalitis/meningitis, and 1308 deaths. The threat of WNV infection has led to the costly implementation of national blood donor screening, as well as vaccine and drug development (*10*). Public outreach campaigns have altered human behavior, including the time spent outdoors, especially by older people, who are at high risk for WNV disease.

The impacts of WNV on wildlife have been yet more severe than those on humans. Millions of birds have died from WNV infection, and regional-scale population declines of >50% have been observed for several species (*11*). The range of taxa that have suffered declines is surprisingly large and includes corvids, chickadees and titmice, wrens, and thrushes (Fig. 1) and probably others. Some populations have recovered after initial declines, whereas others have not (*11*). The

Fig. 1. An American robin (*T. migratorius*) and its nestlings. Robins flourish in human-altered landscapes and appear to play a key role in WNV amplification across many regions of North America. [Photo credit: Bruce Lyon]

Department of Ecology and Evolutionary Biology, University of California, Santa Cruz, CA 95064, USA. E-mail: akilpatr@ucsc.edu

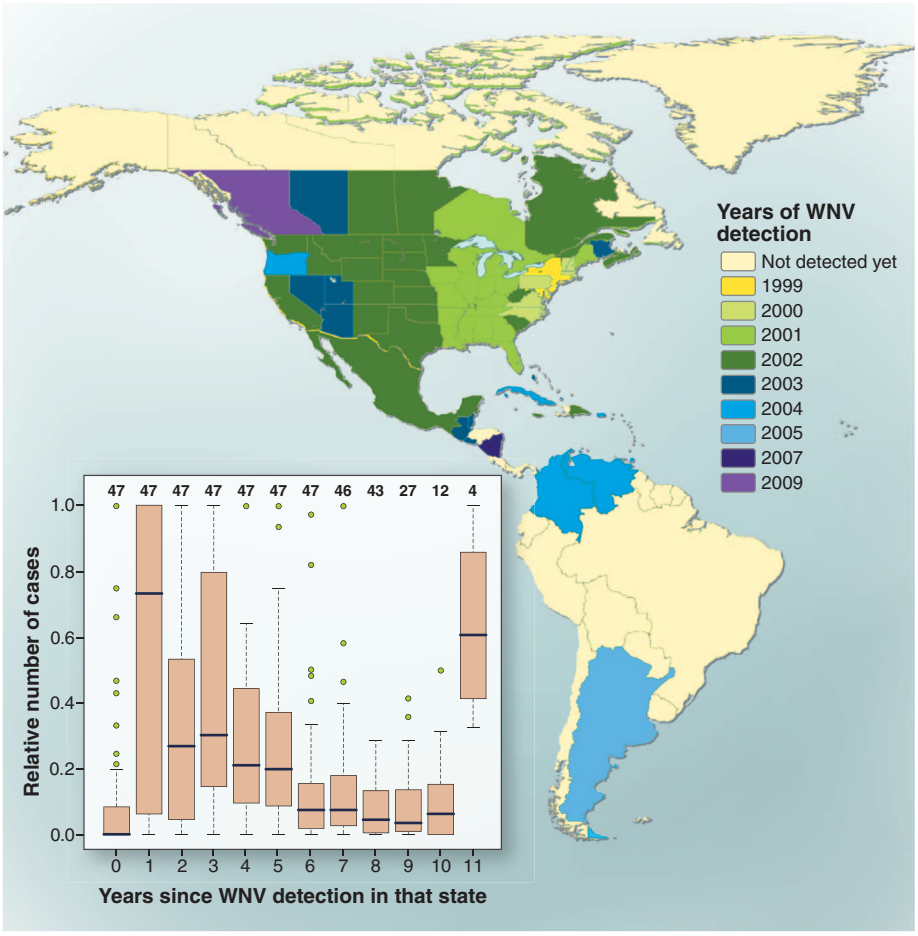

Fig. 2. Spread of WNV throughout the Americas. The map shows the year that WNV was first detected in a state, province, or country. The box plot shows the temporal pattern of WNV incidence at the state level after WNV arrival. The *y* axis shows the relative number of WNV neuroinvasive cases (the fraction of the maximum observed in that state) that occurred in each state in each year, starting with the year WNV was first detected in birds, mosquitoes, humans, or horses. The number of states included in each column is shown above the box.

ecological and economic consequences of these regional declines in bird populations have not yet been elucidated and need further study.

Globalization and the Introduction of Pathogens

The probability of the introduction and establishment of introduced species has been shown to increase with the "propagule pressure," or the rate at which individual organisms are introduced to a new region (Fig. 3) (*5*). The yearly propagule pressure and the pathway by which WNV reached North America in 1999 remain unknown, but several possibilities have been proposed, including mosquitoes being transported by shipping, airplanes, or wind; migratory birds or birds in trade; and humans traveling (*12*). The large and increasing volume of air traffic into New York City over the past five decades makes the transport of infected mosquitoes on an airplane a likely pathway. A close phylogenetic relationship between viruses isolated in New York in 1999 and those circulating in Israel in the previous year suggests a possible Middle East origin (*6*). Trade and travel have also previously introduced key mosquito vectors of WNV, *Culex pipiens* and *C. quinquefasciatus,* as well as vectors for dengue, yellow fever, and chikungunya viruses, such as *Aedes albopictus* and *A. aegypti* (*13*).

What predictions could have been made in 1999 about the outcome of the introduction of WNV into New York City that summer? An answer comes from comparing the ecology of WNV transmission in the Americas with that in Africa and Europe (*14*, *15*).

WNV Ecology in Its Native Range

Studies of endemic WNV transmission in Egypt, Sudan, and South Africa and of Kunjin virus, a subtype of WNV, in Australia show that the virus was most frequently isolated from *Culex* mosquitoes. In Australia, most isolations come from *C. annulirostris*, which is a competent laboratory vector (*16*). In Africa, *C. univittatus* makes up the largest fraction of WNV-infected mosquitoes (*8*, *17*). Interestingly, there is little evidence of WNV infection in *C. pipiens* in South Africa, despite frequent feeding on avian hosts. *C. pipiens* is an important WNV vector in Europe and North America (*15*, *18*). It is possible that the lower WNV infection prevalence observed in *C. pipiens* than in *C. univittatus* can be attributed to its being less susceptible to infection (*17*).

Accurate quantification of the contribution of different host species to viral amplification requires data on mosquito feeding patterns and host abundance from the same place and time, combined with information on the duration and intensity of host infectiousness (*19*). Host abundance and mosquito feeding data have never been collected simultaneously for WNV hosts and vectors in Africa, Asia, Australia, or Europe and have only rarely been collected in North America. As a result, only tentative conclusions can be drawn about the relative importance of host species for WNV outside North America and these largely come from studies of seroprevalence and infectiousness based on viremia (concentration of virus in the blood) observed after experimental infections. In Egypt, hooded crows (*Corvus cornix*) and house sparrows (*Passer domesticus*) had high antibody prevalence and infectiousness (*8*). In South Africa, waterbirds (ducks and rails) and passerine birds in the family Ploceidae (weavers and Old World sparrows, including house sparrows) were most infectious and most frequently had antibodies to WNV (*17*).

The Vectors, Hosts, and Transmission of WNV in the Americas

The most important vectors in North America share some similarities with those in Africa, Europe, and Australia. Although *C. univittatus* is not present in the Americas, *C. pipiens*, *C. quinquefasciatus*, and several other species that take the majority of their blood meals from birds are found in North America, including *C. restuans, C. tarsalis,* and *C. nigripalpus*. Based on their feeding ecology and their vector competence, all these species would be expected to be important in enzootic (bird-to-bird) transmission (*18*, *20*). In addition, their abundance in anthropogenically modified areas points to a significant role in human WNV epidemics.

An important insight was gained in the course of determining the vector species responsible for transmitting WNV from nonhuman animals to humans (i.e., "bridge vectors"). Bridge vectors were initially thought to be mosquito species that fed frequently on mammals (such as *Aedes* mosquitoes), but an integrated analysis of the abundance, infection prevalence, feeding patterns, and vector competence of a wide range of mosquitoes indicated that *C. pipiens* and *C. restuans* mosquitoes, which frequently take <15% of their blood meals from humans, may nonetheless be responsible for the majority of human infections in several regions (*18*, *21*). Their importance results from their higher relative abundance and WNV infection prevalence than the more anthropophilic mosquito species. Applying this integrated approach to other pathogens may simplify targets for vector control, especially when the same species serves as both the bridge and the enzootic vector.

Predicting which avian hosts would be important for WNV transmission in the Americas based on data from Africa or Europe would have failed, because inferences based solely on abundance, infectiousness, or serological (antibody) prevalence can be misleading (*19*). Analyses of data from the mid-Atlantic to Colorado that have combined host abundance and mosquito feeding data with host infectiousness suggested that although introduced house sparrows (*P. domesticus*) and crows (*Corvus* spp.) are abundant and/or highly infectious, they appear to be of minor importance in WNV transmission (*21*–*23*). Crows make up a small fraction of mosquito blood meals, and house sparrows are rarely fed on by mosquitoes relative to their abundance, resulting in few bites per individual and inefficient transmission. Instead, a species of thrush, the American robin (*Turdus migratorius*), appears to be more important in WNV transmission (Fig. 4) (*21*–*23*). This is primarily because 30 to 80% of mosquito feedings by the dominant WNV vectors (*C. pipiens*, *C. restuans*, and *C. tarsalis*) are on robins, despite robins making up only 1 to 20% of the avian communities studied. Questions that arise are why are robins so frequently fed on by mosquitoes, and do robins share a trait with other thrushes that makes them generally important for avian arboviruses? For example, serological studies of the avian Sindbis virus in Sweden indicated higher exposure of thrushes than of any other group (*24*).

Research has also shown that focused feeding on robins amplifies WNV transmission intensity (*22*). This raises the following question: If American robins, which have increased 50 to 100% in abundance over the past 25 years with the urbanization of the North American landscape (*11*), were less abundant, would WNV transmission be lower? It's uncertain, because if mosquito abundance and feeding patterns remain constant, decreasing host abundance increases the vector:host, ratio which increases transmission intensity. In addition, seasonal decreases in robin abundance have been correlated with a shift in mosquito feeding from birds to humans, which increases human WNV infections (*25*). However, in the western and southern United States, where robins are less abundant, they provide only a small fraction of mosquito blood meals, and yet mosquito feeding by another species, *C. quinquefasciatus*, on humans is no greater than in the east (*26*). As a result, the impact of reducing robin abundance on WNV transmission is unknown and would probably depend on the identity, abundance, and infectiousness of alternate sources of mosquito blood meals.

In summary, three important insights have been gained in determining the amplification hosts of WNV in North America. First, abundant hosts

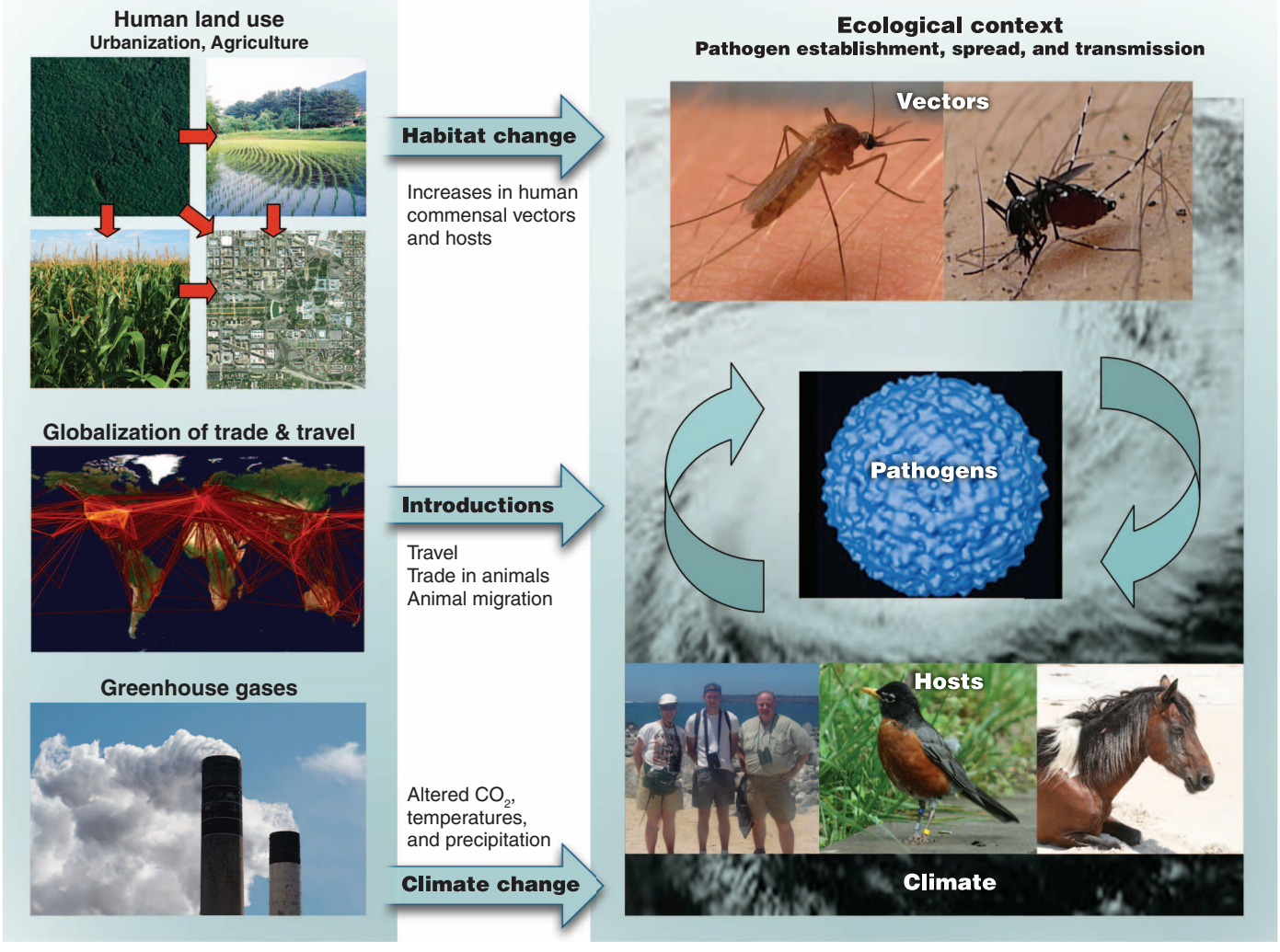

Fig. 3. Anthropogenic processes that facilitate the introduction and establishment of novel pathogens and increase their transmission. Trade, travel, and animal movement introduce new pathogens. Climate, hosts, and the abundance and feeding ecology of vectors determine establishment and transmission intensity. Land use modifies animal communities that serve as hosts and vectors for pathogens, and climate change alters pathogen and vector demographic rates. [Image credits: Google and Tele Atlas (aerial photos); Edward Canda (rice paddy); Photos8.com (cornfield); L. Hufnagel (air traffic map); Dori (dori@merr.info) (smokestacks); Joe Hoyt (left mosquito); Andrew Flemming (right mosquito); Richard Kuhn, Purdue Department of Biological Sciences (virus); NASA (clouds); Marm Kilpatrick (others)]

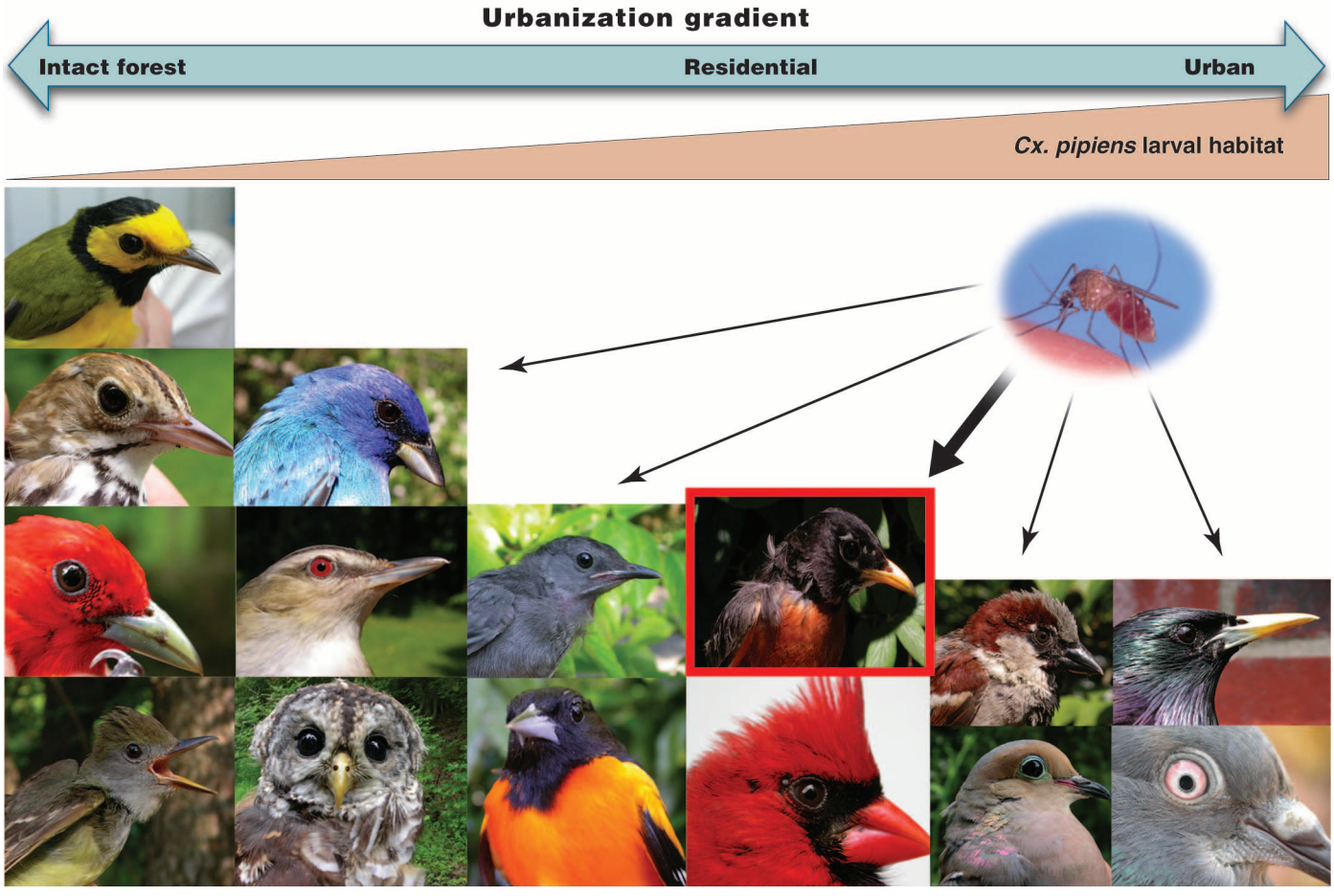

Fig. 4. WNV ecology across an urbanization gradient in the northeastern and midwestern United States. WNV is transmitted primarily by *C. pipiens* mosquitoes among a wide range of birds, but American robins (outlined) are a key amplification host. The diversity of avian hosts decreases with urbanization, whereas *C. pipiens* abundance appears to increase. [Image credit: U.S. Geological Survey (mosquito); Marm Kilpatrick and Ryan Peters (others)]

may be fed on infrequently by vectors, making them less important in transmission. Second, the importance of hosts may be determined more by how frequently mosquitoes feed on them than by variation in their infectiousness. Finally, variation in the abundance of key avian hosts can have unpredictable impacts on transmission, especially to humans.

Hosts and Vectors as Ecological Niches for Pathogens

Studies of WNV amplification hosts show how the feeding patterns and competence of insect vectors and vertebrate hosts create ecological niches for introduced vector-borne pathogens. Characterization of these niches can inform predictions of establishment probability for pathogen introductions (*19*) and augment projections that are frequently based on climatic conditions alone. Such predictions can be used to guide management decisions in allocating resources toward prevention of pathogen introductions (such as vaccine development and testing and quarantine of imported animals). One example of the insight gained from host and vector competence studies comes from an elegant comparison of WNV and St. Louis encephalitis virus (SLEV, a flavivirus native to the Americas) by Reisen *et al.* (*27*), which showed that WNV is more infectious in hosts to biting vectors than SLEV and explained why WNV epidemics are more severe than those caused by SLEV.

Land Use and WNV Transmission

Recent evidence has suggested that at the county scale in eastern and western North America, human WNV incidence increases with urbanization and agriculture, respectively (*28*) (Figs. 3,4). This may result from the habitats used and human-commensal nature of three important WNV mosquito vectors, *C. pipiens*, *C. quinquefasciatus*, and *C. tarsalis*, although the exact mechanisms acting at local scales are not yet known. Nevertheless, the distribution of WNV indicates that it is similar to other pathogens whose transmission is linked with anthropogenic land use and increased abundance of domesticated animals and human-tolerant wildlife species (Figs. 3 and 4). For example, H5N1 avian influenza emerged from poultry intensification; rabies transmission in the Serengeti is maintained by domestic dogs; Lyme disease increases with the fragmentation of forests in eastern North America; and yellow fever, dengue, and chikungunya viruses are all transmitted by the anthropophilic mosquitoes *A. aegypti* and *A. albopictus* (*29*–*33*). Perhaps ecologically based land-use planning, combined with improved development and sanitation, could reduce contact with and the abundance of human-commensal species and hence transmission of their pathogens.

Coevolution of Hosts, Vectors, and Pathogens

Rapid coevolution between WNV and its hosts, vectors, and other pathogens is expected based on reciprocal fitness impacts and in many cases, the lack of shared evolutionary history (*11*, *27*, *34*, *35*). Still, it was somewhat surprising that by 2005, the strain of WNV that was introduced into North America in 1999 (NY99) had been displaced continent-wide by a locally evolved genotype, WN02 (*36*). WN02 was first detected in 2001 and spread continent-wide between 2002 and 2004. Viruses in the WN02 clade consistently differ from NY99 viruses by only three nucleotides that result in one amino acid change. Nonetheless, WN02 viruses are more efficiently transmitted by both *C. pipiens* and *C. tarsalis* mosquitoes, and the difference was found to increase with temperature in the laboratory, as would be expected if the WN02 viruses replicate at a higher rate (*37*, *38*).

The difference between NY99 and WN02 viruses in competence (that is, in magnitude and duration of infectiousness) in avian hosts has not yet been determined. However, another single-stranded RNA virus, Venezuelan equine encephalitis virus, has repeatedly evolved to be able to infect novel hosts and mosquito vectors efficiently, and this shows that host adaption is also possible (*33*).

There may be evolutionary selective pressure for WNV to kill its avian hosts. Individual birds that die from WNV infection have higher viremia, and thus infectiousness to biting mosquitoes, than individuals that survive (*27*, *34*), and host illness from infection decreases host defenses against biting mosquitoes, which would increase vector-host contact rates. Both of these mechanisms increase pathogen fitness by increasing host-to-vector transmission. In addition, in contrast to an assumption made in many models of the evolution of virulence, host death from WNV does not appear to reduce the length of the infectious period of the host: Most avian hosts that survive WNV infection clear virus from their blood between days 4 and 6 after infection, and most individuals that die from WNV infection do so at approximately the same time after infection (*27*, *34*). A key question is whether viral evolution that increased replication and virulence in hosts would have deleterious effects in the vector.

It is also unknown whether North American birds have evolved increased resistance to WNV. This could be determined by repeating WNV laboratory challenge experiments using individuals from the same populations in which resistance was previously measured early in the WNV epidemic (*27*, *34*). Ideally, such studies would include a range of host species or populations that have experienced different selective pressures exerted on them by WNV; for example, in terms of WNV transmission intensity or initial susceptibility to WNV mortality (for example, doves are more resistant than corvids) (*27*, *34*).

Outlook: Unanswered Questions

A key question is will WNV follow the boom-and-bust pattern seen in some plant and animal species invasions (*5*)—are the worst WNV epidemics behind us? WNV epidemics peaked in many states the year after it arrived, with fewer human cases having been observed subsequently (Fig. 2). This reduction in WNV disease has led to reduced research focus and less funding from public health agencies for WNV, and, more recently, less testing for WNV by health care providers.

Reduced transmission may be a product of several factors, including elevated immunity in birds or humans, especially the subset of people most at risk: the homeless and those spending more time outdoors at dusk (*7*). However, annual recruitment of young-of-the-year birds apparently fuels WNV (*39*), which reduces the importance of avian host immunity in suppressing transmission. Instead, it's possible that WNV transmission is modulated primarily by rainfall and temperature, and if so, climatic conditions in 2002 and 2003 were especially suitable. Climate is known to influence many aspects of WNV transmission, including mosquito abundance, biting rate, and survival as well as viral replication within the mosquito (*37*). If WNV transmission is regulated by climate, then severe epidemics could recur, especially if they are facilitated by climate change (Fig. 3). It is notable that the largest number of neuroinvasive WNV cases observed in New York State was in 2010, 11 years after the virus was introduced. Clearly, determining the relative roles of climate versus other factors in year-to-year variation in transmission is important and necessary to predict the long-term trajectory of WNV in North America.

A second unanswered question is why haven't more morbidity and mortality been reported in horses, humans, and birds in tropical regions (*7*, *40*)? Less surveillance is undertaken in these less-developed countries than in North America, and the presence of other diseases, such as dengue, malaria, and Chagas, whose public health impact dwarfs that of WNV, could account for lower reporting, despite similar WNV incidence and illness. Alternatively, cross-protection by antibodies or evolved resistance to illness from other flaviviruses (such as SLEV, dengue, or yellow fever viruses) in humans and horses may decrease illness, without reducing bird-mosquito transmission. In addition, enzootic transmission may be lower in the tropics than in North America, owing to cross-protecting flavivirus antibodies in birds, a mismatch between periods of peak mosquito abundance and susceptible young-of-the-year birds, or lower infectiousness of tropical avian hosts. These mechanisms may be operating simultaneously.

Continual introduction of pathogens to new regions is inevitable in our globally connected planet. It is unclear which vector-borne pathogen will be the next to cross hemispheres, but many viruses of public health concern exist in Africa, Asia, and Europe, including other arthropod-borne viruses such as Japanese encephalitis, Rift Valley fever, tick-borne encephalitis, and chikungunya (*31*). Conversely, there are several pathogens from the Americas that could be introduced into the Old World, including Venezuelan equine encephalitis and SLEV. Insights gained from studying the invasion of WNV can be used to help predict which are the highest-risk pathogens for establishment after cross-hemispheric introduction (*19*). Gaining an understanding of the ecology of zoonotic viruses, combined with fast-developing recombinant vaccine technologies that have already been applied to wildlife (*41*), could form the basis of a strategy to prevent the emergence of newly introduced pathogens.

References and Notes

1. D. Pimentel, R. Zuniga, D. Morrison, *Ecol. Econ.* **52**, 273 (2005).
2. P. K. Anderson *et al.*, *Trends Ecol. Evol.* **19**, 535 (2004).
3. P. Daszak, A. A. Cunningham, A. D. Hyatt, *Science* **287**, 443 (2000).
4. R. N. Mack *et al.*, *Ecol. Appl.* **10**, 689 (2000).
5. A. K. Sakai *et al.*, *Annu. Rev. Ecol. Syst.* **32**, 305 (2001).
6. R. S. Lanciotti *et al.*, *Science* **286**, 2333 (1999).
7. L. R. Petersen, E. B. Hayes, *Med. Clin. North Am.* **92**, 1307, ix (2008).
8. H. S. Hurlbut, F. Rizk, R. M. Taylor, T. H. Work, *Am. J. Trop. Med. Hyg.* **5**, 579 (1956).
9. C. M. Southam, A. E. Moore, *Am. J. Trop. Med. Hyg.* **3**, 19 (1954).
10. D. W. C. Beasley, *Immunotherapy* **3**, 269 (2011).
11. S. L. LaDeau, A. M. Kilpatrick, P. P. Marra, *Nature* **447**, 710 (2007).
12. A. M. Kilpatrick *et al.*, *Conserv. Biol.* **20**, 1224 (2006).
13. L. P. Lounibos, *Annu. Rev. Entomol.* **47**, 233 (2002).
14. Z. Hubálek, J. Halouzka, *Emerg. Infect. Dis.* **5**, 643 (1999).
15. M. V. Fyodorova *et al.*, *J. Med. Entomol.* **43**, 552 (2006).
16. R. A. Hall, J. H. Scherret, J. S. Mackenzie, *Ann. N.Y. Acad. Sci.* **951**, 153 (2001).
17. B. M. McIntosh, P. G. Jupp, D. B. Dickinson, G. M. McGillivray, J. Sweetnam, *S. Afr. J. Med. Sci.* **32**, 1 (1967).
18. A. M. Kilpatrick *et al.*, *Emerg. Infect. Dis.* **11**, 425 (2005).
19. Supporting material is available on *Science* Online.
20. M. J. Turell, M. R. Sardelis, M. L. O'Guinn, D. J. Dohm, in *Japanese Encephalitis and West Nile Viruses Vol. 267 Current Topics in Microbiology and Immunology*, J. Mackenzie, A. Barrett, V. Deubel, Eds. (Springer-Verlag, Berlin, 2002), pp. 241–252.
21. G. L. Hamer *et al.*, *Am. J. Trop. Med. Hyg.* **80**, 268 (2009).
22. A. M. Kilpatrick, P. Daszak, M. J. Jones, P. P. Marra, L. D. Kramer, *Proc. Biol. Sci.* **273**, 2327 (2006).
23. R. Kent, L. Juliusson, M. Weissmann, S. Evans, N. Komar, *J. Med. Entomol.* **46**, 380 (2009).
24. J. O. Lundström, K. M. Lindström, B. Olsen, R. Dufva, D. S. Krakower, *J. Med. Entomol.* **38**, 289 (2001).
25. A. M. Kilpatrick, L. D. Kramer, M. J. Jones, P. P. Marra, P. Daszak, *PLoS Biol.* **4**, e82 (2006).
26. G. Molaei *et al.*, *Am. J. Trop. Med. Hyg.* **83**, 1269 (2010).
27. W. K. Reisen, Y. Fang, V. M. Martinez, *J. Med. Entomol.* **42**, 367 (2005).
28. S. E. Bowden, K. Magori, J. M. Drake, *Am. J. Trop. Med. Hyg.* **84**, 234 (2011).
29. J. L. Kyle, E. Harris, *Annu. Rev. Microbiol.* **62**, 71 (2008).
30. B. F. Allan, F. Keesing, R. S. Ostfeld, *Conserv. Biol.* **17**, 267 (2003).
31. S. C. Weaver, W. K. Reisen, *Antiviral Res.* **85**, 328 (2010).
32. T. Lembo *et al.*, *J. Appl. Ecol.* **45**, 1246 (2008).
33. S. C. Weaver, A. D. T. Barrett, *Nat. Rev. Microbiol.* **2**, 789 (2004).
34. N. Komar *et al.*, *Emerg. Infect. Dis.* **9**, 311 (2003).
35. J. N. Thompson, *Am. Nat.* **153**, S1 (1999).
36. C. T. Davis *et al.*, *Virology* **342**, 252 (2005).
37. A. M. Kilpatrick, M. A. Meola, R. M. Moudy, L. D. Kramer, *PLoS Pathog.* **4**, e1000092 (2008).
38. R. M. Moudy, M. A. Meola, L. L. Morin, G. D. Ebel, L. D. Kramer, *Am. J. Trop. Med. Hyg.* **77**, 365 (2007).
39. G. L. Hamer *et al.*, *Vector Borne Zoonotic Dis.* **8**, 57 (2008).
40. N. Komar, G. G. Clark, *Pan Am. J. Public Health* **19**, 112 (2006).
41. C. A. Russell, D. L. Smith, J. E. Childs, L. A. Real, *PLoS Biol.* **3**, e88 (2005).

Acknowledgments: I thank T. Bogich, K. Koelle, I. Parker, N. Komar, and the Kilpatrick lab for input. NSF grants EF-0914866 and BCS-0826779 and NIH grant 1R01AI090159-01 provided funding.

Supporting Online Material

www.sciencemag.org/cgi/content/full/334/6054/323/DC1
SOM Text
Fig. S1
References

10.1126/science.1201010